# Patient information: Therapy for essential hypertension

Burton D Rose, MD
Harvard Medical School

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This topic will review the appropriate therapy of essential hypertension. The definition of hypertension and the indications for both non-drug and drug therapy are discussed separately. (See "Patient information: Hypertension: What is it, who should be treated, and why" and see "Patient information: Hypertension and diet and weight").

**INTRODUCTION** — Hypertension is the medical term for high blood pressure. Blood pressure refers to the pressure exerted by circulating blood on the inner walls of the arteries. It is measured based upon two values: the arterial pressure both as the heart contracts and as it relaxes between beats (ie, systolic pressure/diastolic pressure).

Most adults with hypertension have what is called essential or primary hypertension, because the cause is not known. A small subset of adults have secondary hypertension, in which an underlying and potentially correctable cause can be identified.

Blood pressure varies naturally over the course of a day, and usually increases with age. In addition, activity affects blood pressure, which rises as a normal response to physical exertion and stress. However, patients with hypertension have high blood pressure even at rest. Untreated hypertension puts strain on the heart and arteries, eventually damaging such tissues, and is a key risk factor for heart failure, heart attack (myocardial infarction), and stroke.

Making appropriate lifestyle changes under a doctor's guidance is an important initial part of any treatment plan for high blood pressure. In some patients, such modifications — such as lowering sodium and alcohol intake, keeping weight in the ideal range, engaging in regular aerobic exercise, and stopping smoking — may be sufficient to control hypertension.

However, many patients also require therapy with medications known as "antihypertensive drugs" to lower the blood pressure. The following is an overview of the different types of drugs that may initially be prescribed for patients who require antihypertensive therapy for essential hypertension. (For information on proper lifestyle modifications and who should receive antihypertensive therapy, see "Patient information: Hypertension and diet and weight" and see "Patient information: Hypertension: What is it, who should be treated, and why").

**ANTIHYPERTENSIVE DRUGS** — There are various classes of antihypertensive agents that are commonly used to reduce high blood pressure. Following is a brief description of the major antihypertensive drug classes, with the generic names of certain medications that are commonly prescribed. Clicking on the name of a drug will call up information on that drug. (Please note that listings of such medications within this review are not all inclusive and are meant for information purposes only.)

Although generally well tolerated, antihypertensive drugs can cause side effects that vary with the specific drug given, dosage, and other factors. In addition, many patients will respond well to one drug but not to another. Therefore, it may take time to determine the right drug(s) and proper dosage levels in your case to most effectively lower blood pressure with a minimum of side effects.

The following discussion includes a general description of the types of side effects that may be associated with certain classes of antihypertensive medications. If you develop any side effects from drug treatment, be sure to inform your doctor so that your medication may be adjusted.

**Diuretics** — Diuretics lower blood pressure mainly by causing the kidneys to increase their excretion of water and sodium, reducing fluid volume throughout the body, and also serve to widen (dilate) blood vessels.

The diuretics used to treat hypertension are thiazides, eg, chlorthalidone, hydrochlorothiazide, and indapamide. In some cases, a potassium-sparing diuretic, eg, amiloride, spironolactone, or triamterene or potassium supplements are given in combination with a thiazide diuretic because the thiazides can produce potassium deficiency due to increased excretion of potassium in the urine.

**Side effects** — Side effects are uncommon at the low doses of thiazide diuretics that are now recommended. Fatigue, dizziness, weakness, and other symptoms can result from the loss of sodium and water and from the loss of potassium. Other symptoms that can occur include reversible impotence and gout attacks. Also, in patients with diabetes, higher doses than currently recommended may make control of blood sugar (glucose) levels more difficult.

**ACE inhibitors** — Angiotensin converting enzyme (ACE) inhibitors block production of the hormone angiotensin II, a compound in the blood that causes narrowing of blood vessels (vasoconstriction) and increases blood pressure. By reducing angiotensin II production, ACE inhibitors allow blood vessels to widen, lowering blood pressure, and improving heart (cardiac) output.

The available ACE inhibitors include benazepril, captopril, enalapril, fosinopril, lisinopril, moexipril, perindopril, quinapril, ramipril, and trandolapril.

**Side effects** — In some patients, ACE inhibitors may cause a persistent dry hacking cough that is reversible with discontinuation of therapy. Less common side effects include dry mouth, nausea, lightheadedness, postural dizziness, rash, muscle pain, or, occasionally, kidney dysfunction.

A potentially serious complication is angioedema, which occurs in 0.1 to 0.7 percent of treated patients. Angioedema refers to the relatively rapid onset over minutes to hours of swelling of the lips, tongue, and throat, which can interfere with breathing. Thus, the development of these symptoms should be considered a medical emergency. Such patients should not continue therapy with an ACE inhibitor.

**Angiotensin II receptor blockers** — The angiotensin II receptor blockers (ARBs) block the effects of angiotensin II on cells in the heart and blood vessels, rather than inhibiting angiotensin II production as with ACE inhibitors.

The available ARBs include candesartan, irbesartan, losartan, telmisartan, and valsartan.

**Side effects** — From the viewpoint of side effects, the main difference between ARBs and ACE inhibitors is that ARBs do not produce cough. A few patients who receive angiotensin II receptor blockers may experience dizziness, drowsiness, headache, nausea, dry mouth, abdominal pain, or other side effects. Angioedema is even less common with ARBs than with ACE inhibitors.

**Calcium channel blockers** — Calcium channel blockers drugs reduce the amount of calcium that enters the smooth muscle in blood vessel walls and heart muscle. Muscle cells require calcium to contract. Thus, by inhibiting the flow of calcium across muscle cell membranes, calcium channel blockers cause muscle cells to relax and blood vessels to dilate, reducing blood pressure as well as reducing the force and rate of the heartbeat.

There are two major categories of calcium channel blockers: drugs known as "dihydropyridines" (including amlodipine, felodipine, isradipine, nicardipine, nifedipine, and nisoldipine); and the nondihydropyridines diltiazem and verapamil. Diltiazem and verapamil are less potent vasodilating agents, but may provide additional effects on cardiac contractility and conduction.

**Side effects** — The side effects that may be seen with calcium channel blockers vary with the specific agent used. Patients who take dihydropyridines may develop headache, dizziness, flushing, nausea, overgrowth of the gum tissue (gingival hyperplasia), or swelling of the extremities (peripheral edema).

The side effects are different with the nondihydropyridines, diltiazem or verapamil. These drugs can cause the heart rate to slow too much. Other side effects include headache and nausea with diltiazem or constipation with verapamil.

**Beta blockers** — Beta blockers block some of the effects of the sympathetic nervous system, which stimulates particular involuntary functions at times of stress, increasing the heart rate and raising blood pressure. Beta blockers lower blood pressure in part by decreasing the rate and force at which the heart pumps blood into the circulation.

The available beta blockers include acebutolol, atenolol, betaxolol, bisoprolol, carteolol, metoprolol, nadolol, penbutolol, pindolol, propranolol, and timolol.

Some beta blockers have combined activity, blocking both the beta and alpha receptors (see next section). These include labetalol and carvedilol.

**Side effects** — Beta blockers may worsen symptoms of asthma, other lung diseases, or abnormal conditions affecting certain blood vessels outside the heart (such as peripheral vascular disease). As a result, they normally are not prescribed for patients with such conditions. In addition, they may mask symptoms of low blood sugar (hypoglycemia) in patients with diabetes who are treated with insulin. Beta blockers can also cause fatigue, dizziness, insomnia, decreased exercise tolerance, a slow heart rate, rash, and cold hands and feet due to reduced blood flow to the limbs.

**Alpha blockers** — Alpha blockers relax or reduce the tone of involuntary (ie, smooth) muscle in the walls of blood vessels (vascular smooth muscle), allowing the vessels to widen, thereby lowering blood pressure. An increase in blood vessel diameter is known as "vasodilation." The available alpha blockers include doxazosin, prazosin, and terazosin.

**Side effects** — Alpha blockers can cause dizziness, particularly when standing up, headache, weakness, drowsiness, postural hypotension, or other side effects. They also may increase the risk of developing heart failure. For these reasons, they are not frequently used for first-line treatment of essential hypertension. A possible exception is in an older man with symptoms related to enlargement of the prostate; such symptoms may be relieved by alpha blocker therapy.

**Direct vasodilators** — Direct vasodilators relax or reduce the tone of blood vessels. The two drugs in this class are hydralazine and minoxidil. Minoxidil is typically used in only severe and resistant hypertension.

**Side effects** — Side effects associated with direct vasodilators include headache, weakness, nausea, constipation, peripheral edema, and rapid heartbeat. These effects are usually minimized by combined therapy with a beta blocker, but are more prominent with minoxidil, which is more powerful. Minoxidil also may cause excessive hair growth. Rogaine, which is used to treat baldness, is the topical preparation of minoxidil.

**Centrally acting agents** — Sympathetic activity can also be reduced by centrally acting agents, such as clonidine, guanabenz, guanfacine, and methyldopa. These drugs, which act in the brain, are now infrequently used because of a worse side effect profile than the drugs listed above.

**Side effects** — Centrally acting drugs can cause postural dizziness, drowsiness, impaired judgment, dry mouth, nausea, constipation, and reversible decrease in sexual function.

**Important** — Before taking any medication, be sure to read all drug labels and any additional information provided by your pharmacist or doctor. It is important that you take the medication exactly as instructed. As mentioned above, if you do develop side effects, speak with your doctor, in order to adjust your dosage or change your medication. In addition, if you experience lightheadedness, dizziness, drowsiness, or impaired judgment when first taking such medication, use caution when driving or engaging in other tasks that require alertness until you know how you are affected by the drug.

**THE PROPER MEDICATION FOR YOU** — Your doctor will take several factors into account when determining which antihypertensive drug should initially be prescribed. In addition to considering the documented effectiveness and potential side effects, your doctor will take into consider your general health, sex, age, and race; the severity of the hypertension; any additional, underlying (coexistent) conditions that are present; and whether particular drugs are inadvisable (ie, contraindicated) in your specific case.

Certain antihypertensive drugs are specifically recommended for the treatment of particular conditions independent of the blood pressure, although such conditions often coexist with hypertension. As examples:

- An ACE inhibitor is given to patients with diabetes mellitus who have increased levels of protein in the urine (proteinuria), heart failure, or a prior heart attack.
- Beta blockers are given to patients with heart failure or a prior heart attack.
- Beta blockers or calcium channel blockers are given for symptom control in patients with angina pectoris, which is temporary chest pain caused by an inadequate oxygen supply to heart muscle in patients with coronary artery disease.

There are also certain antihypertensive agents that are contraindicated in some patients. Some examples include:

- ACE inhibitors and ARBs (and many other medications not used to treat high blood pressure) are contraindicated during pregnancy.

- Beta blockers may be contraindicated in patients with asthma or chronic lung disease.

Finally, certain coexistent conditions may be worsened by treatment with particular antihypertensive drugs. As an example, diuretics can worsen gout.

Thus, a complete history is essential to enable your doctor to determine the appropriate drug therapy for the control of your hypertension. The patient history should include any coexistent conditions, current medications, known drug allergies, and past adverse effects to certain drugs.

**Effectiveness and cardiovascular protection** — Since various antihypertensive medications have documented effectiveness, there is currently no uniform agreement concerning which class of drug should initially be prescribed for the treatment of high blood pressure in most patients. Evidence suggests that each of the four major classes of antihypertensive drugs — diuretics, ACE inhibitors, calcium channel blockers, and beta blockers — is roughly equally effective, resulting in a good response in about 40 to 60 percent of cases. Blood pressure lowering protects against complications such as heart failure, stroke, and a heart attack.

As mentioned above, many patients will respond well to a particular antihypertensive drug but not to another. Therefore, identification of the specific drug class to which you are more likely to respond is a major element in determining which agent your doctor prescribes.

In addition, the use of particular drugs may be associated with better outcomes in certain clinical settings. This was best illustrated in the ALLHAT trial, which is the largest controlled trial ever performed in the treatment of hypertension and had the additional advantage of comparing four different classes of antihypertensive drugs, In this trial of patients at increased risk for coronary artery disease, a low-dose thiazide diuretic produced better outcomes than ACE inhibitors, calcium channel blockers, and beta blockers.

**Recommendations** — For patients with hypertension without any significant underlying disorder or complications (that is, uncomplicated hypertension), we recommend beginning drug therapy with a low dose of a thiazide diuretic, based upon their proven long-term benefit, improved outcomes compared to other drugs, and low cost. This recommendation assumes that a different antihypertensive class is not specifically indicated for the treatment of a coexistent condition.

If low-dose thiazide monotherapy proves ineffective, experts recommend that an ACE inhibitor, ARB, calcium channel blocker, or beta blocker may then be sequentially added or substituted. Evidence suggests that a calcium channel blocker is likely to be most effective in black or elderly patients. However, patients who are unresponsive to a diuretic may have a similar lack of response to a calcium channel blocker; thus, an ACE inhibitor, ARB, or beta blocker may be preferable as second-line antihypertensive therapy.

As noted earlier, these general recommendations for initial therapy are altered for certain patients in whom specific agents may offer particular benefits (eg, both an ACE inhibitor and a beta blocker in patients with heart failure or a prior heart attack). In addition:

- Findings from the ALLHAT trial suggest that a low dose thiazide diuretic in both younger and older patients provides better cardioprotection than an ACE inhibitor or a calcium channel blocker in patients with risk factors for coronary artery disease, including left ventricular hypertrophy (thickening of the heart muscle in response to hypertension), diabetes, current cigarette smoking, lipid abnormalities, or atherosclerotic cardiovascular disease.

A diuretic is also indicated for fluid control in patients with heart failure and in elderly patients with isolated systolic hypertension. In the latter setting, certain long-acting dihydropyridine calcium channel blockers may be an appropriate alternative.

- Based upon a large clinical study known as the "HOPE trial," the United States Food and Drug Administration (FDA) has approved use of the ACE inhibitor ramipril for the reduction of myocardial infarction, stroke, and cardiovascular and overall mortality in patients at high risk for cardiovascular disease. However, because about 90 percent of the study's participants were Caucasian, it remains unclear if these benefits apply to other groups. Furthermore, further examination of the results suggest that the benefit may simply be due to blood pressure lowering rather than a specific effect of the ACE inhibitor.

- An ARB may be appropriately substituted for an ACE inhibitor in patients who develop a persistent dry cough.

- A diuretic is indicated for heart failure and for elderly patients with isolated systolic hypertension. In the latter case, certain long-acting calcium channel blockers (dihydropyridines) may be an appropriate alternative.

- As mentioned above, the use of an alpha blocker (eg, doxazosin, the longest-acting alpha blocker) may be associated with an increased risk of heart failure and therefore generally should not be used as a first-line therapy for hypertension. One possible exception may be in older men who also have symptoms of an enlarged prostate that can be relieved with alpha blocker therapy. These symptoms include weak urine flow, frequent urination, and a sensation of insufficient bladder emptying.

**Combination drug therapy** — If patients have an insufficient response to initial drug treatment, your doctor will probably recommend early addition of a second drug. Alternatives include raising the dosage of the first drug to the recommended maximum dosage or adding a second drug after reaching moderate dosage. Early addition of a second drug may be:

- As or more effective than the other alternatives since many patients who will respond to a particular drug do so at relatively low doses

- Associated with fewer side effects, many of which occur more frequently at higher doses

If two drugs are in fact required, using low-dose therapy with a thiazide diuretic as one of the medications tends to increase the response to other antihypertensive agents. As an example, combining a thiazide diuretic with an ACE inhibitor or a beta blocker or an ACE inhibitor has a "cooperative" (synergistic) effect, controlling blood pressure in up to 85 percent of patients.

**WHERE TO GET MORE INFORMATION** — Your doctor is the best resource for finding out important information related to your particular case. Not all patients with hypertension are alike, and it is important that your situation is evaluated by someone who knows you as a whole person.

This discussion will be updated as needed every four months on our web site (http://www.uptodate.com). Additional topics as well as selected discussions written for healthcare professionals are also available for those who would like more detailed information. Some of the most pertinent include:

Patient Level Information:
Hypertension and diet and weight
Hypertension: What is it; who should be treated; and why

Professional Level Information:
Hypertension: Who should be treated?
Indications for use of specific antihypertensive drugs
Initial evaluation of the hypertensive patient
Overview of hypertension
Resistant hypertension
Screening for renovascular hypertension
Technique of blood pressure measurement in the diagnosis of hypertension
Treatment of isolated systolic hypertension
What is goal blood pressure in treatment of hypertension?
Who should be screened for renovascular or secondary hypertension?
Can therapy be discontinued in well-controlled hypertension?
Diet and hypertension
Prehypertension and borderline hypertension
Patient compliance and the treatment of hypertension
Salt intake and hypertension
The cardiovascular risks of hypertension
Treatment of hypertension in blacks
Treatment of hypertension in diabetes mellitus
Treatment of hypertension in heart failure
Treatment of hypertension in the elderly
Calcium and hypertension
Exercise in the treatment of hypertension
Risk factor reduction (secondary prevention) of cardiovascular disease and stroke
Smoking and hypertension

The prevalence and control of hypertension

A number of other sites on the internet have information about hypertension. Information provided by the National Institutes of Health, national medical societies, and some other well-established organizations are often reliable sources of information, although the frequency with which they are updated is variable.

- National Library of Medicine

(http://www.nlm.nih.gov/medlineplus)

- National Heart, Lung & Blood Institute (NHLBI)

(http://www.nhlbi.nih.gov)

- American Heart Association

(http://www.americanheart.org/)



**REFERENCES**

1. MacMahon, S. Blood pressure and the risk of cardiovascular disease. N Engl J Med 2000; 342:50.

2. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood pressure. The JNC 7 report. JAMA 2003; 289:2560.

3. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). JAMA 2002; 288:2981.

4. Neal, B, MacMahon, S, Chapman, N. Effects of ACE inhibitors, calcium antagonists, and other blood pressure-lowering drugs: results of prospectively designed overviews of randomised trials. Blood Pressure Lowering Treatment Trialists' Collaboration. Lancet 2000; 356:1955.

5. Brown, MJ. Matching the right drug to the right patient in essential hypertension. Heart 2001; 86:113.

6. Materson, BJ, Reda, DJ, Cushman, WC, et al. Single-drug therapy for hypertension in men. a comparison of six antihypertensive agents with placebo (correction - N Engl J Med 1994; 330:1689). N Engl J Med 1993; 328:914.

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# Combination Therapy in the Practical Management of Hypertension

*At a symposium chaired by Addison A. Taylor, MD, PhD, and held in conjunction with the American Academy of Physician Assistants' 32nd Annual Physician Assistant Conference 2004, four specialists in **hypertension**, pharmacology and nephrology presented the latest information on the use of combination **therapy** in the management of **hypertension**. Topics included achievement of target blood pressure goals, protection from target organ damage, and monotherapy versus combination **therapy** outcomes.*

***Speakers***
*Addison A. Taylor, MD, PhD,*
*Program Chair*
*Professor*
*Department of Medicine, Pharmacology,*
*Molecular Physiology and Biophysics*
*Chief, Section of **Hypertension** and Clinical Pharmacology*
*Baylor College of Medicine and Affiliated Hospitals*
*Houston, Texas*

*William J. Elliott, MD, PhD*
*Professor of Preventive Medicine,*
*Internal Medicine, and Pharmacology*
*Rush Medical College*
*Rush University Medical Center*
*Chicago, Illinois*

*Candice R. Pellegrino, MPA-C*
*Physician Assistant*
*Department of Veteran Affairs*
*Michael E. DeBakey Veterans Hospital*
*Instructor*
*Department of Medicine*
*Baylor College of Medicine*
*Houston, Texas*

*Domenic A. Sica, MD*
*Professor of Medicine and Pharmacology*
*Division of Nephrology*
*Chief, Clinical Pharmacology and **Hypertension** Division*
*Virginia Commonwealth University Medical College*
*Richmond, Virginia*

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## Practice-Based Strategies Utilizing Combination Therapy for Optimal Hypertensive Control

"Currently, only one third of patients with **hypertension** in the United States is achieving adequate blood pressure control," said Addison A. Taylor, MD, PhD, Professor, Department of Medicine, Pharmacology, Molecular Physiology and Biophysics; and Chief, Section of **Hypertension** and Clinical Pharmacology, Baylor College of Medicine and Affiliated Hospitals, Houston. In 2003, the Joint National Committee on Detection, Evaluation and Treatment of **Hypertension** (JNC 7) issued new guidelines, noting new blood pressure goals: < 140/90 mmHg for those with uncomplicated **hypertension** and < 130/80 mmHg for those with diabetes or chronic kidney disease (Chobanian et al. *JAMA*. 2003;289:2560). According to Dr. Taylor, "In the vast majority of patients with **hypertension**, **multiple** drugs are required to achieve target blood pressure goals and significantly reduce cardiovascular risk."

According to Dr. Taylor, "A patient who is hypertensive on a single **drug** and is not achieving his or her target blood pressure should be considered for combination antihypertensive **therapy**. In addition, patients who present with comorbidity—such as diabetes, renal disease, or proteinuria—should be considered for first-line combination antihypertensive **therapy**," Dr. Taylor explained. He cautioned that even persons who respond well to antihypertensive monotherapy initially may ultimately require two or three agents to maintain this effect.

### Focusing on Systolic Blood Pressure

Recent study data have emphasized not only the importance of diastolic blood pressure, but also the role of systolic blood pressure in cardiovascular risk. In one meta-analysis of 15,000 people, a reduction in systolic blood pressure was associated with a significant reduction in fatal or nonfatal stroke, fatal or nonfatal coronary events, and cardiovascularmortality (Staessen et al. *Lancet.* 2000;355:865). "Indeed, in persons older than age 55, systolic blood pressure itself has been shown to be the major risk factor for cardiovascular events," Dr. Taylor noted. In the STOP-**Hypertension**-2 trial, aggressive antihypertensive treatment to reduce diastolic blood pressure did not result in the achievement of systolic blood pressure goals, regardless of the **therapy** used. "In contrast, if systolic blood pressure is adequately controlled, diastolic blood pressure is also achieved," Dr. Taylor pointed out (Hansson et al. *Lancet.* 1999;354:1751).

This dynamic was demonstrated in the SOLACE trial, which compared an amlodipine/benazepril combination **therapy** (dihydropyridine calcium channel blocker and ACE inhibitor) with higher-dose amlodipine alone in persons with **hypertension**. Over 12 weeks, the combination **therapy** was consistently associated with significantly better achievement of systolic blood pressure goals. In both treatment groups, the addition of hydrochlorothiazide resulted in an improved response (Neutel et al. *Am J Hypertens*. 2003;16(pt 2):196A).

### Minimizing Side Effects

With combination **therapy**, the goal is not only to enhance treatment efficacy, but also to minimize treatment side effects. "For example, the combination of a potassium-sparing agent and a potassium-depleting agent allows a second **drug** to offset an adverse effect of the first," Dr. Taylor said. In the case of calcium channel blocking agents, peripheral edema is a major side effect of treatment. Indeed, these agents cause arterial dilation, which leads to an increase in capillary pressure and peripheral edema. The addition of an ACE inhibitor promotes efferent postcapillary vasodilation, providing a balance of pressure along the capillaries and a reduction in peripheral edema.

In the SOLACE trial, hypertensive patients taking a calcium channel blocker/ACE inhibitor combination experienced half as much peripheral edema as those receiving higher-dose calcium channel blocker alone (Neutel et al. *Am J Hypertens.* 2003;16 (pt 2): 196A).

In the SELECT trial, hypertensive patients received higher-dose amlodipine alone, higher-dose benazepril alone, or amlodipine/benazepril combined. "The combination approach demonstrated an additive effect, with significantly greater reductions in systolic and diastolic blood pressures compared with either agent alone. In addition, peripheral edema was significantly reduced compared with either monotherapy (Neutel et al. *Am J Hypertens*. 2004; 17(5): 183A).

### Reducing Cardiovascular Risk

A number of factors act to increase a patient's risk for cardiovascular morbidity and mortality. These include insulin resistance, diabetes, dyslipidemia, and **hypertension**. "**Hypertension** itself is associated with independent progression of coronary and peripheral arterial disease, leading to atherosclerosis," Dr. Taylor explained. Left ventricular hypertrophy can lead to cardiac insult, coronary artery disease with myocardial ischemia or infarction, resulting in arrhythmia, loss of muscle function, and heart failure (Dzau et al. *Am Heart J.* 1991;121:1244). "For this reason, our goal is to reduce blood pressure before target organ damage occurs—or to detect this process early when it is potentially reversible," Dr. Taylor said.

In the ALERT study, persons with **hypertension** received either amlodipine/ benazepril or higher-dose amlodipine alone or higher-dose benazepril alone. The combination **therapy** resulted not only in greater reductions in systolic and diastolic blood pressures, but also in significantly improved arterial distensibility than either monotherapy. A significantly greater reduction in left ventricular mass with the combination regimen also suggested a cardiac benefit (Neutel et al. *Am J Hypertens.* 2004;17:37).

In closing, the speaker emphasized the benefits of lower-dose combination antihypertensive **therapy** in blood pressure reduction and target organ protection. He also pointed out the potential advantage of single-pill combination therapies. In one analysis of more than 5000 people, patients taking a single-pill combination antihypertensive regimen demonstrated better adherence than those taking two separate pills (Taylor et al. *Congest Heart Fail.* 2003;9:324). "The data suggest an additive effect with combination antihypertensive **therapy**, allowing greater efficacy and reduced side effects—as well as improved adherence with simplified treatment regimens," Dr. Taylor concluded.

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## Pharmacologic Considerations in the Use of Antihypertensive Combination Therapy

Approximately 58 million Ameri-cans have **hypertension**, and another 45 million meet the definition for prehypertension syndrome. "For many of these individuals, **multiple drug therapy** is needed to achieve systolic and diastolic blood pressure goals," said Domenic A. Sica, MD, Professor of Medicine and Pharmacology, Division of Nephrology; Chief, Clinical Pharmacology and **Hypertension** Division; Virginia Commonwealth University Medical College, in Richmond (Table 1). According to Dr. Sica, co-administration of the various available antihypertensive agents requires an understanding of the pharmacologic basis for each combination.

### The Dose-Response Factor

Numerous classes of antihypertensive agents are available for use in persons with **hypertension**, with many classes acting on **multiple** locations in the body. In many cases, said Dr. Sica, patients with **hypertension** should be considered for first-line **therapy** with a combination of agents rather than monotherapy. "The different agents represent a family of dose-response curves," Dr. Sica explained. "With one small dose escalation in monotherapy, the majority of response is achieved. Any succeeding dose escalation provides a diminishing yield in blood pressure reduction, but a greater increase in side effects. Thus, it is often more effective to give initial combination **therapy** rather than sequential dose titration," he said.

In combining **drug** classes in the treatment of **hypertension**, it is critical that these agents be complementary in action. "The use of a second agent should be additive or synergistic in efficacy, but not in toxic effects," said Dr. Sica.

### Pharmacokinetics and Pharmacodynamics

"The pharmacokinetics of combining antihypertensive agents are seldom of clinical concern; however, an understanding of the pharmacodynamic cross-talk between these agents is paramount," Dr. Sica said. In the treatment of **hypertension**, two main pharmacodynamic interactions are key: that of 1) a diuretic with any other antihypertensive agent and 2) a calcium channel blocker with an ACE inhibitor.

The combination of a diuretic with another antihypertensive agent affords not only a reliable additive effect on blood pressure, but also the minimization of diuretic side effects in persons with **hypertension**. While the exact synergistic mechanism is not completely understood, it appears that the antihypertensive response is greater and longer with higher diuretic doses. The addition of an angiotensin-converting enzyme (ACE) inhibitor to a diuretic regimen, for example, results in a greater reduction in blood pressure and less peri-pheral edema than with monotherapy. "In many cases, initial treatment with a fixed combination antihypertensive regimen—rather than sequential addition of agents—allows for more effective and efficient achievement of blood pressure goals," Dr. Sica said.

"In combining calcium antagonists and ACE inhibitors, the synergistic mechanism likely differs based on whether a dihydropyridine or non-dihydropyridine calcium antagonist is used," Dr. Sica explained. Both drugs work to reduce blood pressure by working on different pathogenic pathways. "In addition, ACE inhibitors act to lessen the counterregulatory response of sympathetic activation—as occurs with dihydropyridine calcium channel blockers," he noted.

In closing, Dr. Sica stressed the critical role of **multiple drug therapy**—including simplified fixed combination regimens—in treating persons with **hypertension**. "This includes first-line combination **therapy** in those who have high blood pressure of 20/10 mmHg or more over goal, diabetes, or chronic kidney disease," he concluded.

**Table 1.**
**Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: Blood Pressure Goals**

| Patient Population | Goal |
|---|---|
| Uncomplicated hypertension | < 140/90 mmHg |
| Hypertension with diabetes or renal disease | < 130/80 mmHg |

Source: Chobanian et al. *JAMA*. 2003;289:2560

## Reducing Clinical Events with Combination Therapy: A Practical Approach

Research evidence suggests a critical role for combination antihypertensive **therapy** in the current and future management of **hypertension** (Table 1). Indeed, the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) now recommends two blood pressure goals: < 140/90 mmHg in those with uncomplicated **hypertension** and < 130/80 mmHg in those with diabetes or chronic kidney disease. The JNC 7 guidelines recommend first-line combination **therapy** for any patient who presents with 20/10 mmHg or more above target blood pressure goals, said William J. Elliott, MD, PhD, Professor of Pre-ventive Medicine, Internal Medicine, and Pharmacology, Rush Medical College, Rush University Medical Center, Chicago. According to Dr. Elliott, several clinical trials also show less target organ damage and fewer cardiovascular events with combination versus monotherapy for **hypertension**.

### Monotherapy versus Combination Therapy

In one meta-regression analysis of 24 clinical trials, only 2.5% of patients receiving mono-**therapy** had a blood pressure reductionof greaterthan 19/9mmHg (Elliott. *Am J Hypertens*. 2002; 15(pt 2):29A). In another meta-analysis, Staessen and colleagues found that differences in cardiovascular events were associated with differences in systolic blood pressure levels (Staessen et al. *Lancet*. 2001;358:1305).

In addition, several trials have found combination **therapy** to be superior to monotherapy in achieving blood pressure reduction and in minimizing side effects. In the randomized FACET study, 380 persons with diabetes received either fosinopril or amlodipine. As cases of uncontrolled blood pressure arose, these patients were allowed to receive both drugs. Over 4 years, those receiving both medications showed significantly fewer major cardiovascular events than either monotherapy group (Tatti et al. *Diabetes Care.* 1998;21:597). In the randomized, multicenter PROGRESS trial, 6105 patients with a history of stroke or TIA in the last 5 years received an ACE inhibitor plus either a diuretic or placebo. Over 4 years, reductions in blood pressure as well as recurrent stroke and cardiovascular events were significantly greater in the combination **therapy** group (PROGRESS. *Lancet*. 2001;358:1033). Similarly, Messerli and colleagues treated persons with **hypertension** with either higher-dose amlodipine or combination amlodipine plus benazepril. This study showed improved reduction in blood pressure and edema with the combination regimen. The ALERT study demonstrated a number of benefits with combination **therapy** over higher-dose monotherapy, including improved blood pressure, reduced arterial stiffness, and regression of left ventricular hypertrophy (Neutel et al. *Am J Hypertens*. 2004; 17:37).

### Future Directions

According to Dr. Elliott, the results of the ACCOMPLISH study are awaited, and will serve to compare cardiovascular morbidity and mortality in persons with systolic **hypertension** who receive either amlodipine/benazepril or benazepril/hydrochlorothiazide combination **therapy**. In closing, Dr. Elliott summarized that the research shows an important role for combination **therapy** as part of current and future antihypertensive treatment regimens, not only for reducing blood pressure but also for reducing the incidence of cardiovascular-associated morbidity and mortality.

**Table 1.**
**Potential Antihypertensive Agent Combinations**

| Agent 1 | Agent 2 (# combinations currently) |
|---|---|
| Diuretic | Any other antihypertensive agent (32) |
| Beta-blocker | Diuretic (8) |
| Calcium channel blocker | ACE inhibitor (4) |
| ACE inhibitor | Diuretic (7); calcium channel blocker (4); ? ARB (0) |
| ARB | Diuretic (6); ? ACE inhibitor (0) |
| Alpha blocker | Diuretic (1) |
| Alpha-2 agonist | Diuretic (7) |

Source: Elliott. *Curr Hypertens Rep*. 2002;4:278.

## Clinical Pearls: The Practical Use of Fixed-Dose Combination Therapy

The physician assistant plays a pivotal role in the identification, diagnosis, and treatment of **hypertension**, a disease that presently affects approximately 58 million Americans, said Candice R. Pellegrino, MPA-C, physician assistant, Department of Veterans Affairs, Michael E. DeBakey Veterans Hospital, and instructor, Department of Medicine, Baylor College of Medicine, Houston. According to Ms. Pellegrino, there is no substitute for a scrutinizing patient history and thorough assessment of each individual patient.

**Patient History and Assessment**
According to Ms. Pellegrino, in addition to a complete patient and family history, a thorough physical examination is critical in identifying and treating **hypertension** effectively. A physical examination should include blood pressure measurements in both arms and legs (including ABI); fundoscopy to rule out retinopathy; assessment for JVD and auscultation of carotids; palpation and auscultation of the heart, abdomen, and femoral arteries; auscultation of the lungs; evaluation for edema; and examination for changes in sensation. It is not uncommon to find blood pressure discrepancies between the upper extremities. When these two measures differ significantly, vascular involvement should be suspected, Ms. Pellegrino said. In addition, the speaker explained, it is helpful to have the patient lie supine for 5 minutes before beginning the examination.

Importantly, in patients in whom a complication or other underlying disease is suspected, appropriate further evaluation is needed. An EKG is performed in those with suspected cardiac involvement, and is followed by a cardiac work-up as appropriate. If PVD is present, other testing for ischemia should be considered. If there is evidence of left ventricular hypertrophy or coronary heart failure, an echo examination may be needed to rule out diastolic dysfunction. It is important to note that **hypertension** must be controlled, before proceeding with non-invasive cardiac ischemia testing, Ms. Pellegrino pointed out.

**Treatment of Hypertension**
The management of **hypertension** requires not only aggressive treatment of the **hypertension** itself, but also of disease risk factors, Ms. Pellegrino explained. **Hypertension** should be treated and monitored aggressively, with frequent office visits, home monitoring, and phone calls.

According to Ms. Pellegrino, most cases of **hypertension** require combination **therapy** to reach blood pressure goals of < 140/90 mmHg in uncomplicated **hypertension** and < 130/80 mmHg in **hypertension** with diabetes or renal disease (Chobanian et al. *JAMA*. 2003; 289:2560). The severity of **hypertension** and presence of underlying comorbidity should guide the clinician in choosing the type and dosage of the antihypertensive agents used, she explained. Recent guidelines indicate use of combination **therapy** in any patient having a blood pressure of > 20/10 mmHg above goal. Effective two-**drug** combinations include: beta blocker/diuretic, ACE inhibitor/diuretic, ACE inhibitor/calcium channel blocker, and ARB/diuretic. Fixed dose combination therapies may offer benefits such as convenient dosing regimens, increased adherence, and lower risk of adverse effects.

Finally, clinicians need to identify and treat risk factors for disease, such as obesity, dyslipidemia, and diabetes, from day one, Ms. Pellegrino said. Thus, initial treatment may involve not only combination antihypertensive **therapy**, but also consideration of antiplatelet treatment, statin **therapy**, and glucose management. Importantly, if a patient shows little or no response to moderate dosing of **multiple** antihypertensive agents and no medical explanation is evident, renal artery stenosis should be considered, Ms. Pellegrino cautioned.

In closing, Ms. Pellegrino noted the importance of the role of physician assistants in providing accurate diagnosis, prompt and aggressive treatment, and effective patient education for **hypertension** and its associated comorbidity and complications. "It is important to remember not to assume non-compliance with antihypertensive **therapy**, to attack this disease quickly with appropriate and often combination therapies, and to target risk factors as well as the disease in this patient population," she concluded.

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